Specification

The Examiner objected to the specification for its use of trademarks. Applicants have amended the specification to remove reflect the proper use of trademarks. Therefore, in view of such amendments to the specification, withdrawal of said rejection is respectfully requested.

Rejection of Claims 35-45 under 35 U.S.C. Section 101

Claims 35-45 are rejected under 35 U.S.C. Section 101 as not being supported by a specific asserted or utility or a well-established utility. The Examiner also states that the credibility of any utility could not be assessed. Applicants respectfully traverse this rejection.

The claimed invention is directed to certain purified polynucleotides, recombinant expression vectors, a cell transfected with said recombinant expression vector, a composition of matter, and to purified polynucleotides that encode certain polypeptides.

In the Office Action, the Examiner states that "[T]here is no evidence to suggest that the claimed polynucleotides are overexpressed in lung tissues." Applicants respectfully submit that this statement by the Examiner is incorrect. As discussed in Example 1 on pages 57-58, EST's corresponding to the consensus sequence of LS147 were found in 35.7% (15 of 42) of lung tissues. EST's corresponding to the consensus sequence of SEQ ID NO:7 (or fragments thereof) were not found in **any** (0 of 610) of the other non-lung tissues. LS147 was only found by Applicants to be expressed in lung tissue. In fact, the consensus sequence or fragment thereof was found more than 35 times more often in lung than in non-lung tissues.

Figure 3, which is a Northern blot and which confirms the data described above in Example 1, shows that the LS147 probe detected an approximately 0.5kb RNA in the lung sample (lane 7) but not in any of the other eleven non-lung RNA samples (lanes 1-6 and 8-12).

As discussed in Applicants last Amendment, the detection of LS147 outside of the lung is diagnostically useful as it serves as an indicator that the host (lung) is in a diseased state. The identification of markers to identify disease in patients is extremely valuable. Several different categories of markers are known that can be used to identify disease. One such category of markers are those that are genes that are expressed in a tissue specific fashion but appear in an inappropriate body compartment when that tissue is diseased (See, specification, page 4, lines 17-33). The expression of a marker in a tissue or body compartment where its normal occurrence is very low or non-existent indicates that the host tissue is diseased and that the marker has escaped from its host tissue. Examples of markers that fall into this category are prostate specific antigen (PSA) and carcinoembryonic antigen (CEA). PSA is normally secreted at high levels into the seminal fluid and is present in very low levels in the blood of men with normal prostates. However, in patients with diseases of the prostate, including benign prostatic hyperplasia (BPH) or adenocarcinoma of the prostate, the level of PSA is markedly elevated in the blood and is a strong indication of disease of the prostate.

Similarly, CEA is a normal component of the inner lining of the colon and is present stool and in blood at low levels in people without disease of the colon. However, in disease of the colon, including inflammatory bowel disease and adenocarcinoma of the colon, the concentration of CEA is markedly elevated in the blood plasma or serum of many patients and is an indicator of disease of that tissue (such as colorectal cancer).

Additionally, like LS147, PSA and CEA are expressed in a few tissues other than the colon and prostate. Nonetheless, these markers are still recognized as useful in the diagnosis of disease of their primary tissue of origin due to their strong tissue selectivity.

Moreover, as discussed in the enclosed Declaration of Dr. Paula Friedman submitted, the specificity of LS147 closely resembles the tissue specificity of PSA and CEA and in fact, LS147 is even more tissue-specific than either CEA and PSA. Therefore, to one of ordinary skill in the art, the presence of LS147 outside of the lung would indicate cancer development of that tissue, just as the presence of CEA and PSA outside of their respective tissues indicates cancer of the colon and prostate, respectively.

35 U.S.C. Section 101 has two purposes. First, 35 U.S.C. Section 101 defines the categories of inventions that are eligible for patent protection. An invention that is not a machine, an article of manufacture, a composition or a process cannot be patented. Second, 35 U.S.C. Section 101 serves to ensure that patents are granted on only those inventions that are "useful". *Manual of Patent Examining Procedure* Section 2107.01 (8th Edition, August 2001). Therefore, to satisfy the requirements of 35 U.S.C. Section 101, an applicant must claim an invention that is statutory subject matter and must show that the claimed invention is "useful" for some purpose, either explicitly or implicitly. *Id.*

To be "useful" for some purpose, the invention must have a specific and substantial utility (i.e. "a practical utility"). A "specific" utility is specific to the subject matter claimed (versus a "general utility" that would be applicable to a broad class of invention). A "substantial utility" defines a "real world" use. Not only must the invention have a specific and substantial utility, but this utility must be credible. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g. test data, affidavits or declarations from experts in the art, patents or printed publications). *Manual of Patent Examining Procedure* Section 2107 (8th Edition, August 2001). An applicant need only provide one

credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement. *Id.*

To properly reject a claimed invention under 35 U.S.C. Section 101, the Examiner must (a) make a *prima facie* showing that the claimed invention lacks utility, and (b) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing (*Manual of Patent Examining Procedure* Section 2107.02 (8th Edition, August 2001)). The Examiner must do more than question the operability of the invention. Specifically, the Examiner must set forth factual reasons that would lead one skilled in the art to question the objective truth of the statement of operability. *Id.*

In view of the above arguments and the evidence presented in previous Amendments, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing that the claimed invention lacks utility. However, even assuming *arguendo* that the Examiner has made a *prima facie* showing that the claimed invention lacks utility, the Examiner has failed to provide a sufficient evidentiary basis for her factual assumptions relied upon in making this showing. Specifically, the Examiner has not provided any evidence refuting or contracting the statements supporting utility made in the Declaration of Dr. Friedman. Clearly, Dr. Friedman is one of ordinary skill in this art.

Therefore, Applicants submit that the rejection of claims 35-45 under 35 U.S.C. Section 101 is improper and should be withdrawn.

Rejection of claims 35-45 Under 35 U.S.C. Section 112, First Paragraph

Claims 68-74 are rejected under 35 U.S.C. Section 112, first paragraph as not being supported by a specific or substantial or credible asserted utility or a well-established utility. Applicants respectfully traverse this rejection.

Applicants herein incorporate by reference their arguments made above in connection with the 35 U.S.C. Section 101 rejection. Therefore, in view of said arguments, Applicants submit that this rejection is improper and should be withdrawn.

Rejection of Claims 39-41 Under 35 U.S.C. Section 112, First Paragraph

Claims 39-41 are rejected under 35 U.S.C. Section 112, first paragraph as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that that the time the application was filed that the inventor had possession of the invention. More specifically, the Examiner has rejected the language "encodes an open reading frame of at least 5 amino acids" and "encoding at least one epitope". In view of the amendments to the claims, Applicants submit that this rejection is now moot and should be withdrawn.

Objection to Claim 45

Claim 45 was objected to as reciting nucleotides "518-284". Applicants have amended claim 45 to remove correct an obvious typographical error. Therefore, Applicants submit that this objection should be withdrawn.

Applicants submit that the claims are now in condition for allowance.

Respectfully submitted,
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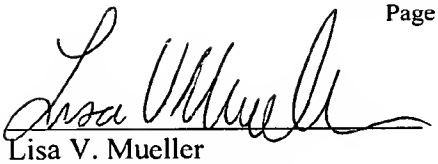

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Version Showing Changes Made

IN THE CLAIMS:

Please amend claims 39, 41 and 45 as follows:

39. (Amended). A recombinant expression vector for use in a desired host comprising:

a nucleic acid sequence [that encodes an open reading frame of at least 5 amino acids, the nucleic acid sequence] selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and nucleotides 51-284 of SEQ ID NO:7,

wherein the open reading frame is operably linked to a control sequence compatible with the desired host, the control sequence selected from the group consisting of promoters, terminators, enhancers, ribosomal binding sites and leader sequences.

41. (Amended). A cell transfected with a nucleic acid sequence [encoding at least one epitope, the nucleic acid sequence] selected from the group consisting of SEQ ID NOS:1-3 and complete complements of SEQ ID NOS:1-3.

45. (Amended). A purified polynucleotide having a sequence selected from the group consisting of nucleotides 51[8]-284 of SEQ ID NO:7 and a complete complement thereof.

IN THE SPECIFICATION:

Please amend page 61, lines 32-35 and page 62, lines 1-2 as follows:

"Non-lung tissues are used as negative controls. The mRNA can be further purified from total RNA by using commercially available kits such as oligo dT cellulose spin columns ([RediCol] REDICOL™ from Pharmacia, Uppsala, Sweden) for the

isolation of poly-adenylated RNA. Total RNA or mRNA can be dissolved in lysis buffer (5 M guanidine thiocyanate, 0.1 M EDTA, pH 7.0) for analysis in the ribonuclease protection assay."

Please amend page 63, lines 20-36 as follows:

"B. Hybridization of Labeled Prove to Target. Frozen tissue is pulverized to powder under liquid nitrogen and 100-500 mg are dissolved in 1 ml of lysis buffer, available as a component of the [Direct Protect] DIRECT PROTECT™ Lysate RNase Protection kit (Ambion, Inc., Austin, TX). Further dissolution can be achieved using a tissue homogenizer. In addition, a dilution series of a known amount of sense strand in mouse liver lysate is made for use as a positive control. Finally, 45 µl of solubilized tissue or diluted sense strand is mixed directly with either: (1) 1 x 10^5 cpm of radioactively labeled probe; or (2) 250 pg of non-isotopically labeled probe in 5 µl of lysis buffer. Hybridization is allowed to proceed overnight at 37°C. See, T. Kaabache et al., Anal. Biochem. 232:225-230 (1995).

C. RNase Digestion. RNA that is not hybridized to probe is removed from the reaction as per the [Direct Protect] DIRECT PROTECT™ protocol using a solution of RNase A and RNase T1 for 30 min at 37°C, followed by removal of RNase by Proteinase K digestion in the presence of sodium sarcosyl. Hybridized fragments protected from digestion are then precipitated by the addition of an equal volume of isopropanol and placed at -70°C for 3 hr. The precipitates are collected by centrifugation at 12,000 x g for 20 min."

Please amend page 69, lines 28-33 as follows:

"Many other detection formats exist which can be used and/or modified by those skilled in the art to detect the presence of amplified or non-amplified LS 147-derived nucleic acid sequences including, but not limited to, ligase chain reaction (LCR, Abbott Laboratories, Abbott Park, IL); Q-beta replicase ([Gene-Trak] GENE-TRAK™,

Naperville, Illinois), branched chain reaction (Chiron, Emeryville, CA) and strand displacement assays (Becton Dickinson, Research Triangle Park, NC)."

Please amend page 74, lines 21-36 and page 75, lines 1-14 as follows:

"A plasmid for the expression of secretable LS147 proteins is constructed by inserting an LS147 polynucleotide sequence from clone 1362407 into the pcDNA3.1/Myc-His vector. (This plasmid will be referred to as pc1362407-M/H.) Prior to construction of pc1362407-M/H, the LS147 cDNA sequence is first cloned into a pCR®-Blunt vector as follows: The LS147 cDNA fragment is generated by PCR using standard procedures using reagents from [Stratagene]STRATAGENE®, Inc. (La Jolla, CA) as directed by the manufacturer. PCR primers are used at a final concentration of 0.5 μM. PCR using 5 U of pfu polymerase ([Stratagene] STRATAGENE®, La Jolla, CA) is performed on the LS147 plasmid template (see Example 2) in a 50 μl reaction for 30 cycles (94°C, 1 min; 65°C, 1.5 min; 72°C, 3 min) followed by an extension cycle of 72°C for 10 min. The sense PCR primer sequence is identical to that found directly upstream of the LS147 insertion site in the pINCY vector. The antisense PCR primer sequence incorporates a 5' NotI restriction sequence and a sequence complementary to the 3' end of the LS147 cDNA directly upstream of the 3'-most in-frame stop codon. Five microliters (5 μl) of the resulting blunted-ended PCR product are ligated into 25 ng of linearized pCR®-Blunt vector (Invitrogen, Carlsbad, CA) interrupting the lethal ccdB gene of the vector. The resulting ligated vector is transformed into TOP10E. coli (Invitrogen, Carlsbad, CA) using a [One Shot] ONE SHOT™ transformation kit (Invitrogen, Carlsbad, CA) following the manufacturer's instructions. The transformed cells are grown on LB-Kan (50 μg/ml kanamycin) selection plates at 37°C. Only cells containing a plasmid with an interrupted ccdB gene will grow after transformation [Grant, S.G.N., PNAS 87:4645-4649 (1990)]. Transformed colonies are picked and grown up in 3 ml of LB-Kan broth at 37°C. Plasmid DNA is isolated by using a [QIAprep] QIAPREP® (Qiagen Inc., Santa Clarita, CA) procedure, as directed by the manufacturer. The DNA is digested with EcoRI or SnaBI, and NotI restriction enzymes

to release the LS147 insert fragment. The fragment is electrophoresed on a 1% [Seakem] SEAKEM® LE agarose/0.5 μg/ml ethidium bromide/TE gel, visualized by UV irradiation, excised and purified using [QIAquick] QIAQUICK™ (Qiagen Inc., Santa Clarita, CA) procedures, as directed by the manufacturer."

Please amend page 75, lines 31-36 and page 76, lines 1-19 as follows:

"B. Transfection of Human Embryonic Kidney Cell 293 Cells. The LS147 expression plasmid described in section A, supra, is retransformed into DH5α™ cells, plated onto LB/ampicillin agar, and grown up in 10 ml of LB/ampicillin broth, as described hereinabove. The plasmid is purified using a [QIAfilter] QIAFILTER™ Maxi kit (Qiagen, Chatsworth, CA) and is transfected into HEK293 cells (F.L. Graham et al., J. Gen. Vir. 36:59-72 (1977)). These cells are available from the A.T.C.C., 12301 Parklawn Drive, Rockville, MD 20852, under Accession No. CRL 1573. Transfection is carried out using the cationic lipofectamine-mediated procedure described by P. Hawley-Nelson et al., Focus 15.73 (1993). Particularly, HEK293 cells are cultured in 10 ml DMEM media supplemented with 10% fetal bovine serum (FBS), L-glutamine (2 mM) and freshly seeded into 100 mm culture plates at a density of 6.5 x10^6 cells per plate. The cells are grown at 37°C to a confluency of between 70% and 80% for transfection. Eight micrograms (8 μg) of plasmid DNA are added to 800 μl of Opti-MEM I® medium (Gibco-BRL, Grand Island, NY), and 48-96 μl of [Lipofectamine] LIPOFECTAMINE™ Reagent (Gibco-BRL, Grand Island, NY) are added to a second 800 μl portion of Opti-MEM I® media. The two solutions are mixed and incubated at room temperature for 15-30 min. After the culture medium is removed from the cells, the cells are washed once with 10 ml of serum-free DMEM. The Opti-MEM I-[Lipofectamine] LIPOFECTAMINE™ -plasmid DNA solution is diluted with 6.4 ml of serum-free DMEM and then overlaid onto the cells. The cells are incubated for 5 hr at 37°C, after which time, an additional 8 ml of DMEM with 10% FBS are added. After 18- 24 hr, the old medium is aspirated, and the cells are overlaid with 5 ml of fresh DMEM with 5%

FBS. Supernatants and cell extracts are analyzed for LS147 gene activity 72 hr after transfection."

Please amend page 77, lines 29-35 as follows:

"E. Coating Microtiter Plates with LS147 Expressed Proteins. Supernatant from a 100 mm plate, as described supra, is diluted in an appropriate volume of PBS. Then, 100 µl of the resulting mixture are placed into each well of a [Reacti-Bind] REACTI-BIND™ metal chelate microtiter plate (Pierce, Rockford, IL), incubated at room temperature while shaking, and then is washed four times with deionized water. The prepared microtiter plate can then be used to screen polyclonal antisera for the presence of LS147 antibodies (see Example 17)."